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Coagulation Abnormalities in the Carbohydrate-Deficient Glycoprotein Syndrome: Case Report and Review of the Literature

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The carbohydrate-deficient glycoprotein syndromes are a group of recently described autosomal recessive, metabolic defects affecting multiple systems. The disorder is caused by inefficient posttranslational glycosylation of glycoproteins. Patients with the syndrome present early in life with psychomotor retardation, seizures, hypotonia, and stroke-like episodes. They also have dysmorphic features including almond-shaped eyes, constant squint, inverted nipples, and buttock fat pads. One of the features of the syndrome is coagulopathy, and we report here a patient who presented with a prolonged activated partial thromboplastin time, and was subsequently diagnosed with the carbohydrate-deficient glycoprotein syndrome. We also summarize the results of five previously published studies of the coagulation system in these patients. Most of the reported patients are deficient in factor XI, protein C, antithrombin III, and protein S. Other coagulation proteins are less frequently affected. Both bleeding and thrombosis have been observed, yet the cause of the stroke-like episodes remains speculative. The carbohydrate-deficient glycoprotein syndrome is an increasingly recognized multisystem disorder affecting hemostasis, and thus will involve clinical hematologists as part of a multidisciplinary team caring for patients with the syndrome. Am. J. Hematol. 60:66–69, 1999.

Key words: carbohydrate-deficient glycoprotein syndrome; antithrombin III deficiency; factor XI deficiency; protein C deficiency

INTRODUCTION

The carbohydrate-deficient glycoprotein syndromes (CDGS) are a group of autosomal recessive multisystem disorders characterized by glycosylation defects of secretory glycoproteins, lysosomal enzymes, and membrane glycoproteins [1–5]. CDGS presents in infancy with neurologic symptoms including psychomotor retardation, seizures, ataxia, hypotonia, and stroke-like episodes. Other organ manifestations may include elevated liver transaminases, retinitis pigmentosa, and skeletal abnormalities, as well as an increased susceptibility to infections. Dysmorphic features include almond-shaped eyes with a constant squint, coarse facial features, inverted nipples, and abnormal fat pads on the buttocks. The basic genetic defect in CDGS type I has been mapped to chromosome 16p and results in a deficiency of phosphomannomutase which leads to inadequate posttranslational glycosylation of many proteins, including coagulation factors and inhibitors [6]. The diagnosis can be established by isoelectric focusing of serum transferrin [7]. The deficiency of sialic acid residues on transferrin causes a cathodal shift because of an increase in asialo- and disialotransferrin and a decrease in penta- and tetrasialotransferrin.

We report herein a child with previously undiagnosed CDGS type I who presented with a coagulopathy, and a review of the literature for the hematologic complications of this disorder.

CASE REPORT

An 8-year-old white male with an undiagnosed multisystem disorder presented to the hematology clinic for

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Fig. 1. Frontal (a) and profile (b) views of the patient demonstrating the typical facial features of carbohydrate-deficient glycoprotein syndrome including almond-shaped eyes, prominent jaw, and cupped ears.

evaluation of a prolonged activated partial thromboplastin time (aPTT). He was the product of a full-term pregnancy and was noted to be developmentally delayed at the age of six months, and developed a seizure disorder at 18 months of age. Dysmorphic features included a prominent jaw, almond-shaped eyes with squint, buttock fat pads, and kyphoscoliosis. In addition, a protein-losing enteropathy and elevated transaminases were noted. As part of his evaluation, a liver biopsy (which was nondiagnostic) was performed without excessive bleeding. Furthermore, he was noted to have episodes of unresponsiveness with transient hemiplegia lasting from minutes to several hours with complete recovery. There is no history of bleeding or thrombotic disorders in any relatives. The ethnicity of the family is French, Native American, and German.

The patient's physical examination revealed a small, wheelchair-bound child with clearly severe motor delay. He had coarse facial features including a prominent jaw, almond-shaped eyes with a constant squint, a deep nasal bridge, and large cupped ears (Fig. 1a,b). There were no bruises, petechiae, or other signs of bleeding on his skin and extremities. His neurologic exam was grossly abnormal. There was poor lip closure with profuse drooling, poor tone, ataxia, athetoid movements, and obvious cognitive delay. His cranial nerve function, muscle strength, and reflexes were normal.

The laboratory evaluation revealed the following: Prothrombin time (PT), 13.2 sec (11.3–13.9); aPTT, 56.7 sec (19.3–32.7); bleeding time, 7.5 min (<9 min); factor (F)VIII, 43% (55–145%); FIX, 73% (70–140%); FXI, 11% (65–145%); FXII, 93% (60–160%); von Willebrand factor antigen, 71% (21–172%); ristocetin cofactor, 62% (55–190%); protein C (PC) activity, 38% (68–144%); PC antigen, 27% (68–144%), and antithrombin (AT)III activity, 37% (84–124%). Carbohydrate-deficient transferrin revealed 4% pentasialotransferrin (13–23%), 28% tetrasialotransferrin (38–49%), 11% triasialotransferrin (17–31%), 45% disialotransferrin (2–15%), 4% monosialotransferrin (0–6%), and 8% asialotransferrin (0–5%), confirming the diagnosis of CDGS.

DISCUSSION

CDGS is a recently described autosomal recessive disorder of glycoprotein metabolism [1–5]. Patients with the disorder have a complex, multisystemic disorder due to a deficiency of N-linked glycans of glycoproteins. These

N-linked glycoproteins are important to many biochemical systems of the body. Hemostatic factors and inhibitors are posttranslationally modified by glycosylation and multiple functional deficiencies of these proteins are present in CDGS. There are five reports in the literature regarding the coagulation abnormalities in CDGS [8–12].

In a study by Van Geet and Jaeken [8], all nine children tested had deficiencies of FXI, PC, and ATIII. The FXI levels ranged from 5% in a one month old to 44% in an eight year old. The levels of PC and ATIII were similarly depressed and also widely variable. The levels of these factors in the parents were normal except for one father who had a PC level of 54%. Protein S and heparin cofactor II were diminished in five of nine patients. The presence or absence of symptoms were not reported. Okamoto et al. [9] reported a family with two affected members both of whom had prolonged aPTTs and were deficient in FXI and PC, and one was deficient in ATIII and FIX as well. Neither patient had any episodes of bleeding or thrombosis. Three children were studied by Iijima et al. [10], and all were deficient in PC, PS, ATIII, and α-2 plasminogen inhibitor. They were not tested for FXI. One patient developed disseminated intravascular coagulation (DIC) and arterial thrombosis in a hand that was cannulated with an arterial catheter. Stibler et al. [11] performed the largest study to date on the coagulation system of patients with CDGS. Three of 13 patients had prolongations of the aPTT; 8 of 14 patients were deficient in FXI; 8 of 13 were deficient in PC activity; 11 of 14 were deficient in ATIII activity, and 14 of 15 were deficient in ATIII antigen. In addition, they also reported deficiencies in FII (8/12; 0/12 < 50% activity), FV (5/14), FVII (1/13), FIX (1/13), and FX (9/12; 3/12 < 50% activity). No explanation was given for the normal aPTTs in most of these patients. In this report, six patients had hemorrhagic symptoms, two of whom also developed deep vein thrombosis (DVT). Two patients had stroke-like episodes and another had DVT. Fiumara et al. [12] studied four patients and their parents from two families. All four patients and both mothers had a prolonged PT and aPTT, and were deficient in FXI, PC antigen, and PS antigen, while the patients were deficient in ATIII activity and antigen. Two patients from the same family were also deficient in FII, FV, FVII, FVIII, and FIX. Their mothers were also deficient in FVIII. FVIII was also low in both children and the mother from the other family. Two patients, one from each family, suffered from stroke-like episodes.

Table I shows the results of all the studies combined. It is clear that deficiencies in FXI, PC, and ATIII are nearly uniform. Twenty-three of 29 patients tested were deficient in FXI, 22/31 were deficient in PC activity, 28/32 and 22/24 were deficient in ATIII activity and antigen, respectively. There were significant differences reported with regards to the other factors. All four patients from the study by Fiumara et al. were deficient in FVIII; however, none of the nine patients Jaeken et al. tested were deficient. Stibler et al. found deficiencies in FII, FV, FVII, FIX, and FX, whereas Jaeken found these to be normal. Finally, deficiencies of the antifibrinolytic enzyme, α-2 plasminogen inhibitor were found in 3/3 patients in the study by Iijima et al., but none of the 13 patients tested by Stibler had this deficiency. Of 24 patients questioned for symptoms, six had hemorrhage, three had DVT, four had stroke-like episodes, and one had DIC. None of the parents were symptomatic.

TABLE I. Summary of the Abnormal Coagulation Studies in CDGS From Previous Publications*

Coagulation test	Frequency of abnormal results	References
PT	4/9	9,10,12
aPTT	9/22	9–12
Fibrinogen	0/20	9–12
FII	10/30, 0/30 < 50%	8–12
FV	7/32, 6/32 < 50%	8–12
FVII	3/28 ,1/28 < 50%	8,9,11,12
FVIII	4/15, 3/15 < 50%	8,9,12
FIX	5/31, 4/31 < 50%	8–12
FX	11/30, 3/30 < 50%	8–12
FXI	23/29	8,9,11,12
FXII	2/15[a]	8,9,12
FXIII	0/9	8
vWF	1/12[b]	11
PCAc	22/31	8–12
PCAg	6/9	9,10,12
PSAc	2/3	10
PSAg (total)	3/3	10
PSAg (free)	13/16	8,10,12
ATIIIAc	28/32	8–12
ATIIIAg	22/24	9–12
HCII	5/9	8
Plasminogen	0/20	9,10,11
α-2 PIAc	3/16	10,11
α-2 PIAg	3/3	10

*CDGS, carbohydrate-deficient glycoprotein syndromes; PT, prothrombin time; aPTT, activated partial thromboplastin time; F, factor; vWF, von Willebrand factor; PC, protein C; PS, protein S; ATIII, anti-thrombin III; HCII, heparin cofactor II; α-2 PI, α-2 plasminogen inhibitor; Ac, activity; Ag, antigen.
[a]Familial FXII deficiency.
[b]Familial von Willebrand's disease.

The coagulation proteins undergo significant post-translational glycosylation. As such, in patients with CDGS, the coagulation factors are underglycosylated. The reason why the activity of only certain coagulation proteins is affected is unclear. One could hypothesize that for FXI, ATIII, and PC, the addition of sugar moieties is essential for function, whereas for others it is less important and still others not required at all.

The question of how these patients should be treated with regards to their coagulopathy is difficult to answer in light of the fact that they have deficiencies in both procoagulant proteins and anticoagulant proteins. In addition, patients have been reported to have catastrophic bleeding as well as thrombosis, and many patients suffer

from stroke-like episodes. Whether these stroke-like episodes are due to the deficiencies in ATIII, PC, and PS remains to be answered. Furthermore, in light of these patients' multiple medical problems, it is likely that they will require various diagnostic and therapeutic procedures. Are these patients at increased risk for postsurgical bleeding or thrombosis? More experience will be necessary to answer this question.

Our patient underwent open liver biopsy at the age of two years (prior to the time the syndrome was recognized), and did not receive any factor replacement therapy. Open liver biopsy is a moderate hemostatic stress, and in spite of a severe deficiency of FXI, our patient did not bleed excessively. Perhaps his deficiencies in PC and ATIII had a protective effect.

CONCLUSIONS

We have presented the case of a patient with CDGS type I, a new syndrome with hematologic manifestations that will involve clinical hematologists as part of a multidisciplinary team to care for these patients. Further studies and experience with such patients will enable us to determine how these patients should be managed with regards to factor replacement therapy and anticoagulation.

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